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*Edited by* **RAYMOND E. KIRK**
*Head, Department of Chemistry, Polytechnic Institute of Brooklyn*

*and* **DONALD F. OTHMER**
*Head, Department of Chemical Engineering, Polytechnic Institute of Brooklyn*

*Assistant Editors*
**JANET D. SCOTT** *and* **ANTHONY STANDEN**

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J. H. Arnold and Helmut Pichler

**FULLER'S EARTH.**   See *Clays (fuller's earth)*.

**FULMINATES; FULMINIC ACID,** HONC.   See *Cyanides*, Vol. **4**, p. 681; *Explosives (high)*, Vol. **6**, p. 10.

**FUMARIC ACID,** HOOCCH:CHCOOH.   See *Fermentation; Maleic acid*.

**FUMES.**   See *Smokes and fumes*.

**FUMIGACIN,** $C_{32}H_{44}O_8$; **FUMIGATIN,** $C_8H_8O_4$.   See *Antibiotics*, Vol. **2**, pp. 22, 29, 34.

**FUMIGANTS; FUMIGATION.**   See *Antiseptics*, Vol. **2**, p. 80; *Insecticides; Sterilization, disinfection, fumigation*.

**FUNGI.**   See *Fungicides; Microorganisms*.

## FUNGICIDES

The word "fungicide" comes from the Latin *fungus*, and the Latin *caedo*, to kill, hence, a fungus killer. In practice the term has come to denote a wider concept. A fungicide is a chemical that will kill, inhibit, or inactivate a fungus so that it does not grow. Some modern investigators are tending to substitute "fungitoxic" or "antifungal" for "fungicidal." See also *Antiseptics*; *Sterilization*. In general, the term carries a practical connotation, that is, a chemical that prevents fungi or molds from ravaging cloth, wood, plants, animals, and humans, or whatever else they attack. The word *prevents* is significant in this definition. With very few exceptions, present-day fungicides are protective. A piece of wood or an apple, once rotted, is beyond recovery, whatever the fungicide used. The fungicide must be applied before the infection has occurred or certainly before it has progressed very far. An antifungal compound must be very stable and resist action by heat, sunlight, rain, and oxidation, particularly since fungi are favored by high humidity. The compound must also have an affinity for the substance treated so that it will cling readily to it, but at the same time it must have at least some degree of solubility, in order to be able to exert a toxic action on the fungus.

Two general theories of fungicidal action have been advanced, the oligodynamic theory, and the suicide theory. The oligodynamic theory (action by a few) postulates that the insoluble residue of fungicides slowly liberates a few molecules into the water where the fungus is growing. These few molecules pass into the fungus along with its foodstuffs. Eventually enough accumulates to poison the fungus. Some experimental evidence exists to support the theory. The suicide theory, on the other hand, postulates that the fungus plays an active role. When a fungus grows, it excretes various substances into the medium, and it is postulated that these excretory products dissolve the fungicidal compound or convert it to a soluble compound that is toxic. According to this theory, the fungus, in effect, makes its own poison.

## AGRICULTURAL FUNGICIDES

Agricultural fungicides, together with insecticides, are the basis of an extensive manufacturing and distributing industry. Some crops like potatoes, apples, and citrus would disappear from the market without fungicides. For want of a satisfactory fungicide, Irish farmers harvested practically no potatoes for three straight years in the middle of the last century, and the resulting famine started large-scale migration from Ireland to the U.S.

Consumption figures for agricultural fungicides are difficult to come by. The U.S. Department of Commerce estimated the consumption of sulfur as a fungicide in 1947 as 79,000 tons. They estimated also that the use of dithiocarbamic acid derivatives climbed from 2,000 tons in 1947 to 4,000 tons in 1948. Groggins of the War Food Administration estimated that 50,000 tons of copper calculated as copper sulfate pentahydrate were needed in agriculture in 1945. McCallan of the Boyce Thompson Institute has estimated the annual consumption of formaldehyde and organic mercurials as 1,000 tons each.

In modern agriculture, fungicides are applied not only to foliage to control diseases like the potato blight, but also to seeds, to soil, and to fruits themselves. Fungicides are generally applied in water suspension with hydraulic sprayers. Sometimes they are applied as dusts, with extenders such as clay or talc. Dusting is more rapid,

but generally less effective than spraying. Ninety-nine per cent or more of the fungicides used are applied to the surface of plant parts to prevent the entry of parasites. In fact, the concept has so dominated the thinking, that the alternative, internal application, has all but been ignored. Internal treatment offers real promise as Stoddard and Dimond have shown (11). The types of compound used will probably be different, however. Water solubility will be a desirable rather than an undesirable property. See also *Insecticides*; *Sprays*.

The first agricultural fungicides used were elemental sulfur and compounds of heavy metals such as mercury and copper. They dominated the field until the 1930's, when adequate laboratory screening techniques were devised. During the 1940's, the flow of new compounds increased to a torrent, and it will probably increase further. Primary screening by modern technique involves a system, comprising fungus and chemical, in which spores and test compound are brought together in distilled water. By varying the dose of compound and reading the response in percentage of spores inhibited, one can generate a dosage–response curve. This curve can be reduced to a straight line by proper transformations (5). This line has two properties—position and slope. Position measures potency; slope indicates mechanism. Position can be used to measure the importance of particle size, of formulation, and of subtractive interference by other ingredients. Slope shows whether two compounds kill by the same or by a different mechanism. For example, the slope of the dosage–response curve of *o*-aminodiphenyl, $C_6H_5C_6H_4NH_2$, is steeper than that of *o*-hydroxydiphenyl (*o*-phenylphenol), $C_6H_5C_6H_4OH$. This suggests that the compounds act differently on the fungus. The fungicide chemist, therefore, has a biological tool to tell him whether he is making progress down a new road or only farther along the old road. Secondary screening techniques involve fungus, chemical, and host. See also *Antiseptics (testing)*.

At present there are three major groups of fungicides: heavy metals, elemental sulfur and polysulfides, and organic compounds. Each of these will be discussed in order.

## Heavy-Metal Fungicides

Much research has been done to discover the best heavy metal for use in fungicides. None has yet proved generally superior to copper. Copper has many advantages. It is widely toxic to fungi, and not widely toxic to host plants nor to humans. It is reasonably cheap, and forms types of salts that resist rain and other weather factors. See *Copper compounds*.

The fungicidal action of copper was discovered late in the 18th century when copper sulfate was used to treat wheat seed to kill the spores of the smut fungus. Its use was not extended to foliage for another hundred years because copper sulfate was toxic to foliage. Late in the 19th century, a Frenchman of Bordeaux discovered that the black-rot disease of grape was absent from foliage treated with an unpleasant-looking mess of copper sulfate and lime applied to prevent pilferage. Lime (calcium hydroxide) antidoted the injurious action of copper sulfate on foliage and Bordeaux mixture was born. Bordeaux mixture, which has probably saved more food for the world than any other pesticide discovered prior to DDT, is a chemist's nightmare. Page has been piled on page of reports discussing the chemistry of the mixture. At first, the reaction was believed to be simple:

$$CuSO_4 + Ca(OH)_2 \longrightarrow Cu(OH)_2 + CaSO_4$$

but many later chemical studies threw doubt upon this interpretation (9). The chief difficulty is that 25 per cent less calcium hydroxide is required than indicated from stoichiometric considerations. This result leads most investigators to write the formula for the final mixture as $4CuO.SO_3.3H_2O$. There is some doubt as to the degree of hydration, however. This compound may be described as copper trioxysulfate or more commonly as tribasic copper sulfate. Martin has returned to the original formula contending that the $Cu(OH)_2$ is stabilized by the calcium sulfate (9).

A few "ready-made" basic salts of copper have been introduced to compete with Bordeaux mixture as sprays. They have the distinct advantage of freedom from lime, which is toxic to many vegetable plants. At various times, copper silicate, copper zeolite, cuprous oxide, copper oxychloride, tribasic copper sulfate, and a double salt of basic copper chloride and basic sulfate have been used. These copper compounds are rapidly disappearing from the vegetable and potato fields with the rise of dithiocarbamate salts. The last two are still used extensively on cherries, however. Copper carbonate and cuprous oxide are the important "ready-made" compounds of copper that are used as seed treatments. Copper carbonate has had a wide and long-continued use as a treatment for the stinking smut disease of wheat since its original proposal by Darnell-Smith in 1917. In recent years, the trend has been toward replacing the copper carbonate with organic mercury materials. Cuprous oxide was introduced by Horsfall in 1932 as a vegetable-seed treatment. Its use rapidly expanded during the 1930's on such crops as spinach, peas, beets, and tomatoes. Its use declined just as spectacularly in the 1940's following the discovery of the fungitoxic action of chloranil in 1938 and the introduction of tetramethylthiuram disulfide by Tisdale. Cuprous oxide also has been widely used as a foliage spray, but the usage is declining.

Mercury has had a long vogue in plant pathology. Corrosive sublimate (mercuric chloride, $HgCl_2$) still is used extensively on seeds. Riehm, the German plant pathologist, following Ehrlich's work on organic arsenic for syphilis, developed o-(chloromercuri)phenol, $C_6H_4(OH)HgCl$, for seed treatment, and this was followed by other organic mercury compounds, notably ethylmercuric chloride, $C_2H_5HgCl$, ethylmercuric phosphate, and phenylmercuric cyanamide. These are or have been widely used in seed treatment especially against the cereal smuts. 2-Chloro-4-(hydroxymercuri)-phenol was one of the first recognized seed protectants. A coating over the seed prevents attack by soil fungi. Zinc 2,4,5-trichlorophenate, $(C_6H_2Cl_3O)_2Zn$, is finding a place in the seed treatment of cotton for seed- and soil-borne diseases.

Owing to the rise of organic fungicides in the 1940's, the heavy-metal compounds have tended to drop into the background. Harry and his co-workers have used non-Daltonian complexes of chromium and other metals (3). The chemistry of these materials is unusual, for they seem to be intermediate between true molecular compounds and mechanical mixtures. A complex of copper, zinc, and chromium (hexavalent) shows promise as a potato fungicide, but it has as yet received little commercial adoption. Another complex, containing most of the heavy metals ever investigated as fungicides, has the composition $6CdO.100CaO.25CuO.10ZnO.25SO_3.10CrO_3.170H_2O$. This seems to be specific for turf diseases. Its success has stimulated further search for cadmium compounds.

### Sulfur and Calcium Polysulfide

Sulfur has been used as a fungicide since the times of Homer, at least. It is quite toxic to many fungi, not very toxic to higher plants, and hardly toxic at all to warm-

blooded animals. It is very insoluble, resistant to light, but rather weak in capacity to cling to treated tissue. For practical use sulfur must be made "wettable" by means of various surface-active compounds. If it is rendered too wettable, it washes off the plant too easily; if not enough, it rises to the top of the spray tank and does not pass through the pump. Moreover, the particle size must be small if the sulfur is to perform satisfactorily. One answer to these problems that prevailed for a hundred years was known as "lime sulfur." Lime sulfur is prepared by boiling sulfur and calcium oxide together to form calcium polysulfides, which may be represented $Ca=S_n=S$. This substance, consisting of mixed polysulfides, is much more toxic to spores than elemental sulfur and it is likewise much more toxic to the host plants. Lime sulfur on standing decomposes giving elemental sulfur with a very minute particle size, which resists rainfall better than "wettable sulfur." Sulfur finds its most successful use on rosaceous plants like apples and other noncitrus fruits. It is a less active fungicide than copper, but the phytotoxicity is so much lower that it is preferred. Sulfur largely replaced Bordeaux mixture on fruit in the early part of the 20th century.

## Organic Fungicides

The first successful organic fungicide was formaldehyde (*q.v.*), which was put forward in the 1890's as a treatment for seed of the white potato. On a molar basis it is a rather low-grade toxicant, but its volatility is an advantage in soil fumigation, because the toxicant disappears from the soil and the seeds can then be planted. Formaldehyde is also used for fumigating storage houses. Formerly, it had some use as a seed treatment. Chloropicrin (*q.v.*), $CCl_3NO_2$, has also been used for a soil fumigant. It is much more active than formaldehyde.
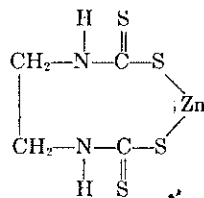
The first organic fungicide for foliage was ferric dimethyldithiocarbamate, $[(CH_3)_2NCSS]_3Fe$, the first of a long series of dithiocarbamates, some of which enjoy wide popularity as foliage protectants. The specificity of these compounds for different diseases is striking. The basic synthesis for the group is the reaction of the proper amine with carbon disulfide in the presence of an alkali. The simplest example is sodium dimethyldithiocarbamate, $(CH_3)_2NCSSNa$, which is produced as follows:

$$HN(CH_3)_2 + CS_2 + NaOH \longrightarrow (CH_3)_2NCSSNa + H_2O$$
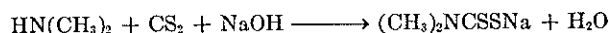
Sodium dimethyldithiocarbamate is a good spore killer but it is of no value on foliage because it is so soluble that it washes off in the first rain. The ferric salt is much used as a spray for the scab and rust diseases on apples, for it seems almost to be a specific for rust diseases. It is also used for blue mold of tobacco. The compound is tenacious and stable. Its coal-black color detracts somewhat from the success of the compound because it downgrades the fruit. The zinc salt, $[(CH_3)_2NCSS]_2Zn$, cannot be used on apples because of fruit russeting due to the zinc. Compounds of this type seem to be specific for the anthracnose group of diseases. Many other metallic salts of the dimethylamine derivatives have been tried, but none has been as successful as the iron and zinc salts.

A more recent introduction in the dithiocarbamate field is disodium ethylenebisdithiocarbamate, $NaSSCNH(CH_2)_2NHCSSNa$. This compound is by far the most fungitoxic on the molar basis of any dithiocarbamate so far produced. It is made from ethylenediamine instead of dimethylamine. Although the compound is water-soluble, it has a curious capacity to cling to a treated surface and resist rainfall. This is about the only fungicide so far known with that property. Disodium ethylenebis-

dithiocarbamate reached the stage of commercial adoption despite being very unstable. The compound would probably have been abandoned had not a lucky accident resulted in showing the value of zinc sulfate in stabilizing the compound (4). In present practice, a slight molar excess of zinc sulfate is added to the spray tank just before use. The probable structure of the zinc salt is:

$$
\begin{array}{c}
\overset{\displaystyle H}{\underset{\displaystyle |}{}} \quad \overset{\displaystyle S}{\underset{\displaystyle \|}{}} \\
CH_2-N-C-S \\
| \qquad\qquad \diagdown \\
| \qquad\qquad\qquad Zn \\
| \qquad\qquad \diagup \\
CH_2-N-C-S \\
| \quad \| \\
H \quad S
\end{array}
$$

Despite their close similarity in composition and even in structure, zinc ethylenebisdithiocarbamate and zinc dimethyldithiocarbamate have decidedly different fungicidal properties. Zinc ethylenebisdithiocarbamate has a much wider range of fungitoxic action than zinc dimethyldithiocarbamate. Thus the former will control both the *Alternaria* target spot and the *Phytophthora* late blight of tomato; the latter will control only the target-spot disease. Presumably the two compounds affect different biological systems. Tank-mixed zinc ethylenebisdithiocarbamate is rapidly replacing copper compounds on the potato crop. The compound seems almost specific for the diseases of potato and tomato.

A fungicide related to the dithiocarbamates is tetramethylthiuram disulfide, $[(CH_3)_2NCSS]_2$. This compound is an excellent foliage spray, but it is much more expensive than the dithiocarbamates and hence is seldom used on foliage except on turf for the brown-patch disease. It has found a place for itself as a dust seed treatment for vegetable and corn seeds. It has the disadvantage of being a skin irritant, to such an extent that workmen have refused to use it. However, a machine has been invented to treat seeds with a slurry of the compound, and in this manner the irritant effects are avoided.

Chloranil (I), tetrachloro-*p*-benzoquinone, is a powerful fungicide. It may be significant that it is a pro-oxidant; copper can act as a pro-oxidant, and the compound was selected for testing on the hypothesis that there may be a connection between pro-oxidant action and fungicidal action. The compound turned out to have especially desirable qualities as a seed protectant for legume seeds. It prevents their decay by soil-borne microorganisms. Considering that the compound is used at the low dose of 0.25% by weight of seed (depending upon size), the tonnage sold is impressive. The compound practically drove copper out of the field for seed protection. Chloranil is not satisfactory as a foliage spray, presumably because it undergoes photochemical oxidation to chloranilic acid which is soluble and washes off. The compound must be limited to seed treatment where it can remain in the dark.

The only other commercial quinone fungicide is 2,3-dichloro-1,4-naphthoquinone (II). It shows a very wide range of fungitoxicity and gives field control of a variety of fungus diseases. It seems to be the least specific in its action of any of the new organic fungicides. It promises to reach the stage of large-scale commercial adoption on apples, especially in the northern apple belts. On the other hand, the compound shows more tendency toward phytotoxicity than the others. It gives excellent control, for example, of the dreaded late blight disease of potatoes, but at the same time may reduce the yield of potatoes. The compound seems to affect the physiology of the
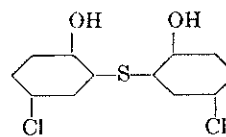
potato plant so that the starch made in the leaves does not move to the roots to make tubers. It may produce some speckling of leaves and fruits of apples. It has been claimed that some of this injury may be avoided by adding magnesium sulfate to the spray fluid. Another serious disadvantage is the skin rash produced on some operators by the compound.
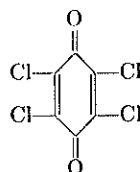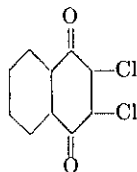


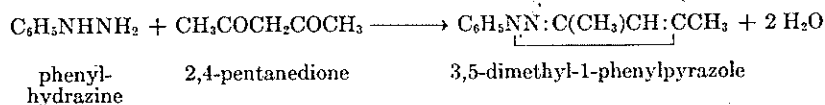(I) Chloranil  (II) 2,3-Dichloro-1,4-naphthoquinone  (III) 2,2'-Thiobis(4-chlorophenol)

Heterocyclic compounds known variously as imidazolines or glyoxalidines, obtained by reaction of ethylenediamine with fatty acids, were introduced by Wellman and associates (12). The most promising member of the series so far appears to be 2-*n*-heptadecylglyoxalidine, $NHCH_2CH_2N:CC_{17}H_{35}$ (see *Ethylene amines*). It is used commercially for leaf spot on cherries and has been tested on a large scale for scab on apples.

Next to sulfur, nitrogen appears to be the most important constituent element of an organic fungicide (other than carbon and hydrogen, of course). Often this nitrogen occurs in a heterocyclic system. Chlorination of organic compounds seems to be much less important in fungicides than in insecticides. Perhaps the earliest heterocyclic-nitrogen fungicide was 8-quinolinol (8-hydroxyquinoline), $HOC_9H_6N$, and 8-quinolinol sulfate. The sulfate is not used to protect foliage because it is too soluble, but it has found some use as an internal fungicide (chemotherapeutant) for Dutch elm disease (1). In the mid-thirties the French plant pathologists recommended the copper complex of 8-hydroxyquinoline for foliage use. Recently, the compound has been reintroduced in America for the purpose. Its probable commercial adoption is small, however, because of cost and because the copper is toxic to copper-sensitive plants.

In late 1949, McNew and Sundholm published on the fungicidal action of pyrazole derivatives (10). The compounds are typically prepared by treating hydrazine or phenylhydrazine with a $\beta$-diketone compound as follows:

$$C_6H_5NHNH_2 + CH_3COCH_2COCH_3 \longrightarrow C_6H_5NN:C(CH_3)CH:CCH_3 + 2 H_2O$$

phenyl-        2,4-pentanedione        3,5-dimethyl-1-phenylpyrazole
hydrazine

Substitution of a nitroso group in the 4-position enhances the activity of the pyrazole, especially when the molecule also contains an aryl group in the 1-position. These compounds are said to be probably "the most effective organic fungicides revealed to date." Chemically, it is interesting to note the similarities to the glyoxalidines. In both cases we have 5-membered rings with two nitrogens in the ring. In the pyrazoles the two nitrogens are joined; in the glyoxalidines they are separated by a carbon atom. On the basis of present data, the two types cannot be said to act similarly on the biological systems of the fungi. Pyrazoles probably will not become commercially important until some way is found of eliminating the serious hazard of skin irritation pre-

sented by all those that have been tested up to the present. 2-Aminopyridine, $NH_2C_5H_4N$, has recently been mentioned as a possible compound for dipping picked oranges to prevent rot in storage and transit.

Quaternary ammonium compounds (*q.v.*) depend apparently for their fungicidal action on the presence of tetracovalent nitrogen, either in a straight chain or as a hetero-atom in a ring system. An example is laurylisoquinolinium bromide, which has a very high fungistatic level but, together with other quaternary ammonium compounds, is too soluble in water to be effective as a protectant. The only quaternary ammonium compound that has found practical use in agriculture is mercuric triethanol-ammonium lactate. This compound, although water-soluble, has some protective value. Probably its success lies, however, in its ability to penetrate diseased leaf spots and kill out the infecting fungus, thus curing the leaf.

Diphenyl, like most hydrocarbons, has only a negligible fungitoxicity. Occasionally, it has been used to dip oranges to prevent rot in storage. The insertion of bridges between the rings seems to add little to the fungitoxicity, but hydroxyl or amine substitutions in the rings add toxicity. 2,2'-Dihydroxy-5,5'-dichlorodiphenylmethane (2,2'-methylenebis(4-chlorophenol)) has been used as a mildew-proofer of military material (8), but it seems to have little possibility for plant-disease control. If, however, a sulfur bridge is substituted for the methane bridge between the two rings, a potent fungicide for apple scab appears, 2,2'-thiobis(4-chlorophenol) (III). This compound has not yet reached the stage of commercial adoption. In some tests the compound russets the apple fruit.

### Biological Activity of the Compounds

If ever the development of fungicides is to emerge from its present empirical fog, more knowledge of the biological activity must be obtained. A brief summary of present knowledge follows: Three basic types of action are postulated at present, protein precipitation, interference with enzyme systems, and antagonism of essential metabolites in the cell. The compounds which presumably act in these three ways are: (*1*) protein precipitation—formaldehyde, heavy metals; (*2*) interference with sulfhydryl enzymes—heavy metals, quinones; interference with metal-containing enzymes—sulfur, hydrogen sulfide, dithiocarbamates, probably other organic sulfur compounds, hydroxyquinoline derivatives, and any other nitrogen compound capable of forming chelate complexes with metals; (*3*) interference with essential metabolites— quinones, copper, nitroso pyrazoles and other strong oxidants, which probably interfere with oxidation–reduction systems involving such compounds as cysteine, and ascorbic acid. Horsfall and Zentmyer (6) showed that most reagents for aldehydes, sugars, amines, or amino acids were fungitoxic.

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J. G. HORSFALL

## INDUSTRIAL FUNGICIDES

Fungicides for the sterilization and preservation of industrial products have not had as long a history as those used for combating plant diseases, nor has the study of industrial fungicides been as intensive. Most of the compounds currently in use are of recent development and represent stop-gap measures awaiting new and more effective fungicides. A compilation of industrial fungicides is a heterogeneous conglomerate. Relatively few are generally applicable for a diversity of items, as is the case with Bordeaux mixture in plant pathology and DDT in insect control. The chief cause for the restricted application of a given industrial fungicide lies in the varied nature and end uses of the respective items involved. Often the secondary properties of the fungicide under consideration, such as toxicity to humans, reaction with metals, leaching by rain, catalytic effect on actinic degradation, incompatibility with other compounds on the material, cost, and ease of application, weigh as heavily as the ability to inhibit microbiological growth per se. For this reason the principal compounds in use today as industrial fungicides are here grouped according to the industrial products involved, rather than according to the chemical nature of the fungicide. See also *Food chemicals*.

**Adhesives.** Synthetic resin adhesives such as urea-formaldehyde are relatively resistant to fungal attack. Adhesives and glues of starch, casein, dextrin, or bone origin are extremely susceptible. For the inhibition of microbiological growth in this group, $\beta$-naphthol, $C_{10}H_7OH$, in concentrations of approximately one per cent is fairly satisfactory. Organic mercurials, $RHgX$, have also been suggested. In this case, however, particular care must be exercised on account of their human toxicity, and they should not be used in adhesives for gummed labels or items which come into continuous or intimate contact with the skin.

**Air.** Many compounds have been investigated for the control of acute respiratory infections in industry by reducing the number of air-borne pathogenic microorganisms. Although these organisms are in most cases bacterial rather than fungal, the subject may well be considered here. Sprays of glycols, lactic acid, and hypochlorous acid have been developed. Propylene glycol, $CH_3CHOHCH_2OH$, is used in concentrations of approximately 1 gram per 3000 liters of air. Although this compound is not toxic to man at a concentration of 0.3 mg. per liter for several hours' exposure, the treated air is characterized by a stale and unpleasant odor. The glycol also condenses on the walls and windows, leaving a sticky film. Triethylene glycol, $(HOCH_2CH_2OCH_2)_2$, is a more effective disinfectant than propylene glycol, and is also superior in that it does not condense as readily on the walls. With both compounds, however, the treated air is uncomfortable to patients during warm weather. Despite the effectiveness of glycolization in lowering the bacterial count in air, there are not sufficient rigorous data

at the present time to make a definite statement as to the desirability of these disinfecting treatments.   See *Air conditioning*.

**Cork.**   Resin-bonded cork is far less susceptible to microbiological growth than glue–glycerol-bonded cork.   For the latter case, one of the most effective fungicides available is *p*-nitrophenol, $C_6H_4(NO_2)(OH)$.   This is added in concentrations of about 2%.   Salicylanilide, zinc dimethyldithiocarbamate, and 2,2'-methylenebis(4-chlorophenol) have also been used but so far found to be less effective.   All of these compounds can be applied either in organic solvents or paraffin waxes.

**Cotton Fabrics and Cordage.**   During the 1940's, over a thousand compounds were tested as possible fungicides on cotton fabrics and cordage.   Many have been found satisfactory for suppressing the mildewing of fabrics during storage or shipment.   Of these, the most popular has been salicylanilide, $HOC_6H_4CONHC_6H_5$, which has the advantage of being colorless and odorless.   It can be applied either from organic solvents or in the form of its sodium salt in aqueous solutions.   A final concentration of 0.1–0.5% based on the weight of the cloth is usually sufficient.   Pentachlorophenol, tetrachlorophenol, and their sodium salts are also satisfactory for this purpose.   However, when the treated fabrics are used outdoors, subject to the rain, sunlight, and wind, or in contact with the ground, these fungicides are nondurable and ineffective.   The two compounds at present preferred are copper naphthenate and the copper derivative of 8-hydroxyquinoline.   Copper naphthenate (see *Driers and metallic soaps*) displays good fungicidal action at concentrations of about 0.5%.   It is applied either from organic solvents or aqueous emulsions.   Because of its unpleasant odor, dark green color, skin irritation, tackiness, and deteriorative effects on certain metals, the use of copper naphthenate has been restricted to areas where these disadvantages are not important considerations.   Although not as effective from a purely mildew-proofing viewpoint, zinc naphthenate has been used to overcome some of these objections.

The most promising compound emerging from the extensive testing program carried out during World War II is the copper derivative of 8-hydroxyquinoline, $Cu(OC_9H_6N)_2$ (see *Quinoline*).   This compound is odorless, light yellowish green, and highly insoluble in most solvents.   For some time the insolubility of the compound has been an underlying difficulty in application techniques in ordinary textile mills.   Recently, however, the compound has been put into solution by the addition of solubilizing agents, and its use has become widespread.   When added to cotton fabrics in concentrations of 0.1–0.5%, it provides high antimildewing activity in outdoor exposures.

Other popular fungicides include cuprammonium hydroxide, phenyl mercurials, pyridyl mercurials, trimethyloctadecylammonium pentachlorophenate, and 2,2'-methylenebis(4-chlorophenol).

**Leather.**   In the preservation of skins for museum purposes, soaking for 15–30 minutes in a 1% solution of sodium fluosilicate, $Na_2SiF_6$, will stop bacterial growth on freshly flayed skin.   Phenylmercuric acetate, $C_6H_5HgOOCCH_3$, and other phenyl mercurials are similarly used in the tanning industry to stop microbiological decay in the cure and soak water.   As a class, the phenyl mercurials are stable compounds.   Their solubility is dependent largely on the anion.   Thus, the oleate and stearate are much more soluble in nonpolar solvents than the acetate and chloride.   The organic mercurials are more corrosive to galvanized iron and aluminum than other fungicides and will cause blistering on human skin if not washed off.   For the prevention of

mildewing on finished leather other compounds have been employed. So far the most suitable are the copper complex of 8-hydroxyquinoline and *p*-nitrophenol, either alone or in combination with pentachlorophenol. The compounds can be applied either in shoe waxes or from organic solutions. A typical formulation for the purpose is: 2% *p*-nitrophenol, 2% pentachlorophenol, 10% neatsfoot oil, 16% cyclohexanone, and 70% perchloroethylene.

**Lenses and Prisms.** In the tropics, fungi have been known to etch lenses and prisms in optical equipment. The growth can be controlled through the use of radium foil in the form of a collar around the lens in binoculars and transits. However, the relative scarcity and high cost forced this method of protection to give way to other fungicides. Short-term protection has been given by *m*-cresyl (*m*-tolyl) acetate, $CH_3C_6H_4OOCCH_3$, and ethylmercuric thiosalicylate, $C_2H_5HgOOCC_6H_4SH$. Because of their deteriorative effects on metals, however, these two compounds must be used in small concentrations.

**Paints and Lacquers.** Fungi grow well under humid conditions on linseed oil- and casein-based paints. Local discoloration results, which may become widespread. Phenylmercuric oleate, $C_6H_5HgOOC(CH_2)_7CH:CH(CH_2)_7CH_3$, appears to be the best antimildewing agent for house paints to date. As low as 0.02% mercury by weight is sufficient. Other compounds that have been studied include phenylmercuric acetate, phenylmercuric naphthenate, chlorinated phenols, salicylanilide, zinc dimethyldithiocarbamate, and the copper complex of 8-hydroxyquinoline. Actually, in many cases the pigments themselves, such as zinc, copper, lead, and chromium oxides, are effective fungicides.

**Pharmaceuticals and Cosmetics.** Alcohol exerts a good preservative action in pharmaceutical preparations in concentrations above 15%. The same action is exhibited by 50% glycerol and 50% sucrose solutions. Frequently, when these are absent or present in lower concentrations, antimicrobial agents are added; the glycerol $\alpha$-ether of *p*-chlorophenol is an example. Its use is limited, however, by its lingering burning taste to nonoral uses. Alkyl and benzyl esters of *p*-hydroxybenzoic acid in concentrations of 0.05–0.15% are more widely used, particularly in cold creams, lotions, hair-waving fluids, and soaps. Others employed include eugenol, propylene glycol, phenylmercuric nitrate, phenol, and cresol derivatives.

**Plastics.** Synthetic polymers themselves are not susceptible to attack by fungi and bacteria. Many of the plasticizers used in formulating plastic materials, however, are excellent supporters of microbiological growth. This is particularly true of fatty acid esters and castor-oil derivatives. In such cases, attempts have been made to prevent microbiological growth by the addition of fungicides. So far there is no compound adopted for wide general use. Laboratory results reported by various workers indicate promise in the organic mercurials and the copper derivative of 8-hydroxyquinoline.

**Water.** The principal agent used in water purification is chlorine, which is added either as the free liquid or as calcium and sodium hypochlorites. For the purification of drinking water between 3–8 pounds of chlorine per million gallons of water is usually sufficient. Sometimes ammonia is added just before the chlorine in weight ratios of 1:4 for the purpose of decreasing the unpleasant taste of chlorine. In swimming pools the amount of free chlorine is kept below 0.5 p.p.m. Chlorine is noticeable in concentrations of 10 p.p.m. in air and becomes irritating to the lungs and membranes of the nose and throat with increasing concentrations. Its germicidal effect is influenced by

many factors. Alkaline conditions as well as the presence of sulfur or iron suppress its activity.

On a much smaller scale and for small volumes of water, Halazone (*p*-dichloro-sulfamylbenzoic acid) and succinchlorimide have been employed. The former does not impart an evident taste even at concentrations of 4 p.p.m. Diglycine hydro-iodide, bromides, and silver preparations have also been tried, although with less success. Quaternary ammonium derivatives, such as Phemerol chloride (benzyldimethyl-{2-[2-(*p*-1,1,3,3-tetramethylbutylphenoxy)ethoxy]ethyl}ammonium chloride), are quite satisfactory in disinfecting drinking water for poultry in concentrations of 1 p.p.m. See also *Water, industrial and municipal.*

**Wood.** Coal-tar creosote has been the standard preservative, particularly for railroad ties. It is a distillate from coal tar boiling between 200 and 400°C. and is made up of a host of hydrocarbons and heterocyclic derivatives. Compounds identi-fied in creosote include cresols, naphthols, toluene, benzene, phenanthrene, fluorene, pyridine, and quinoline. The mixture is applied most effectively by tank dips, either in the open or under pressure. It can also be painted or sprayed onto the wood. Railroad ties have a life expectancy of 5.5 years, but this is increased fivefold by creosote treatment.

Less effective are water-soluble derivatives, the principal one in the U.S. being zinc chloride. Because of its ready leachability by water, attempts have been made to increase its durability. Chromated zinc chloride is one of the chief products from this development. This is a mixture of 4 parts of zinc chloride to 1 part of sodium chromate. Sodium fluoride, copper sulfate, mercuric chloride, and arsenic salts have also been tried in a minor way.

Organic compounds applied from 5% solution in organic solvents include tetra- and pentachlorophenol, chloro-*o*-phenylphenol, and β-naphthol. The effectiveness of these treatments is difficult to assess at the present time in view of the insufficiency of service records. In general, they are not as efficient as creosote from a preservative standpoint. However, there are uses in which the ready flammability, the objection-able odor, the stickiness, the toxicity, and the incompatibility with paints of creosote are highly undesirable. In such cases, some of these compounds may find quite a demand. Frequently, mixtures are preferred. A typical treatment of this kind is the hot-bath dip for telephone poles. The poles are soaked for several hours in hot creo-sote, followed by a similar length of time in a cold bath of 5% pentachlorophenol in a 4:1 mixture of petroleum and creosote.

**Wool** is as rapidly digested by microorganisms as cotton, particularly by species pathogenic to man. So far, relatively few investigations have been carried out on the mildew-proofing of woolen fabrics. Slime resulting from bacterial growth on paper-makers' felt is effectively controlled by a 12-hour soaking in phenylmercuric acetate or chlorinated phenol solutions. Mixing of copper oleate in the paper pulp itself is another technique employed for the same purpose. For felt gaskets, copper penta-chlorophenate, phenylmercuric oleate, the copper derivative of 8-hydroxyquinoline, 2,2'-methylenebis(4-chlorophenol), and zinc dimethyldithiocarbamate have shown considerable promise in concentrations of about 1%.

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R. G. H. Siu

**FURAL, 2-FURALDEHYDE,** $C_4H_3OCHO$.  See *Furfural*.

**FURAN,** $O.CH:CH.CH:CH$.  See *Furfural*.

**FURANOSES.**  See *Carbohydrates*, Vol. **2**, p. 874.

## FURFURAL AND OTHER FURAN COMPOUNDS

Furfural is the most important of the compounds containing the five-membered furan ring (*R.I.* 111) (I), characterized by one oxygen atom.  It is an aldehyde (II) with the —CHO group in the 2(or $\alpha$)-position, and it is obtained on a large scale from



(I) Furan.    (II) Furfural    (III) Furfuryl alcohol    (IV) Furoic acid
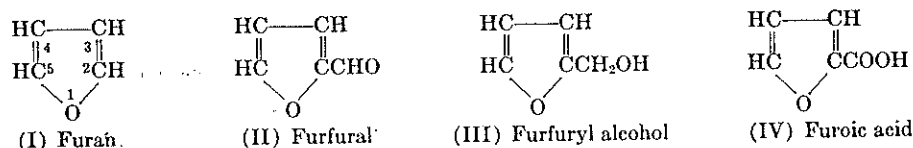
corncobs, oat hulls, cottonseed hulls, and other agricultural residues containing pentosans, which yield pentoses on hydrolysis:



pentose    furfural
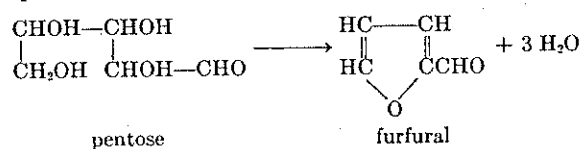
The corresponding alcohol, furfuryl alcohol (III), and acid, furoic acid (IV), as well as furan itself are also commercial products.  More important in commercial volume than the acid and furan, however, are two saturated derivatives, tetrahydrofuran (V) and tetrahydrofurfuryl alcohol (VI).



(V) Tetrahydrofuran          (VI) Tetrahydrofurfuryl alcohol

The polyfunctional nature of the furan nucleus, which may be considered a dienic ether, leads to an interesting group of reactions. This nucleus, with its conjugated unsaturation, is usually classed as aromatic and possesses a relatively high order of stabilization due to resonance. Substitution takes place preferentially in the $\alpha(2$ or $5)$-positions. However, the aromatic character of the furan nucleus is very weak, as shown by its ability to undergo additions almost as readily as an aliphatic diene such as vinyl ether or butadiene. Thus furan, alkylfurans, and the simple halofurans, among others, react readily with maleic anhydride to form the expected Diels-Alder adducts, 3,6-endoxotetrahydrophthalic anhydrides (31). Furthermore, furan and alkylfurans are susceptible of hydrolytic fission. 2,5-Dimethylfuran, for example, on hydrolysis in aqueous acetic acid in the presence of a little sulfuric acid yields 88% of acetonylacetone (2,5-hexanedione), $CH_3COCH_2CH_2COCH_3$. Ring opening can also be effected by catalytic oxidation in the vapor phase.

## Furfural

Furfural (2-furaldehyde (*C.A.*), fural, 2-furancarboxaldehyde, furfuraldehyde, furole), $C_4H_3OCHO$, formula weight 96.08, is a water-white liquid when freshly distilled, but darkens on standing in contact with air. The principal uses for furfural are as an intermediate in the manufacture of hexamethylenediamine (employed in the manufacture of nylon), and compounds containing the furan ring (including furfuryl alcohol, tetrahydrofurfuryl alcohol, furan, and tetrahydrofuran); as a selective solvent for separating saturated from unsaturated compounds in petroleum lubricating oil, gas oil, and Diesel fuel, as well as vegetable oil; as an ingredient in resins, especially of the phenol-aldehyde types; as a decolorizing agent for wood rosin; as a resin solvent and wetting agent in the manufacture of abrasive wheels and brake linings; and in the extractive distillation of butadiene and other $C_4$ hydrocarbons for the manufacture of synthetic rubber.

The discovery of furfural is credited to Dobereiner, whose work was first reported in 1832. During the next 90 years, about 2000 investigations were reported in the literature, but in 1920 there was still no commercial production of furfural. During research undertaken in that year to produce an improved live-stock feed by acid-digesting oat hulls, Brownlee discovered furfural in the vapors from the digester (3). The first drum of furfural was produced by The Quaker Oats Company in February 1922, at Cedar Rapids, Iowa, and the first important commercial use of furfural was by Stokes and Smith Company (now Borden Company) for the production of phenolic resin. Other uses were soon developed, and the demands for furfural of the synthetic rubber program during World War II, added to other wartime demands, made necessary a considerable expansion in production capacity. Laboratory work on furan compounds has continued apace, and today there are some 4000–5000 scientific articles as well as some 3200 patents on furan compounds or their applications. About one-sixth of these patents deal with resins in some form.

### PHYSICAL AND CHEMICAL PROPERTIES

*Constants.* Some of the physical properties of furfural and other furan compounds are given in Table I. Additional properties of furfural are as follows: vapor pressure:

| Temperature, °C | 39.9 | 92.3 | 120.3 | 131.6 | 140.2 | 154.4 | 159.0 | 160.9 | 163.8 | 170.6 |
|---|---|---|---|---|---|---|---|---|---|---|
| Vapor pressure, mm. Hg | 8 | 69 | 214 | 310 | 411 | 625 | 707 | 744 | 812 | 966 |